REMARKS

On behalf of the Applicants, the undersigned representative appreciates the R-1 telephonic interviews granted on March 5 and April 6, 2004. It is believed that the interviews clarified some of the issues in this case.

Claims 2-20, 22-24, 26, 34, 36-37, 68, 69 and newly added Claim 70 are in the application.

Claims 2-20, 22-24, 26, 34, 36-37, 68 and 69 stand rejected under 35 U.S.C. §112 first paragraph on the grounds that the specification, while being enabling for compositions containing the active ingredients recited in Claim 38, "does not reasonably provide enablement for 'rapidly precipitating drug…'".

Claims 2-20, 22-24, 26, 34, 36-37, 68 and 69 stand rejected under 35 U.S.C. §103(a) "as being unpatentable over Makooi-Morehead, U.S. Patent 6 238 695 in view of Elger (U.S. Patent 4 844 407), to the extent they read on Claim 38."

THE REJECTION OF CLAIMS 2-20, 22-24, 26, 34, 36-38, 68 AND 69 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The initial burden of showing non-enablement is on the Examiner. To meet this burden the examiner must establish a reasonable basis to question the enablement provided for the claimed invention. MPEP 2164.04; *In re Wright*, 27 USPQ2nd 1510,1513 (Fed. Cir. 1993). He has failed to meet his burden in the instant case. In making this new ground of rejection, the Examiner advanced three arguments in support of his reasons why the claims were not enabled:

> "The instant claims merely calls for the use of a trial and error to attempt to find a compound that will perform the recited limitation. The instant specification first fails to identify any commonality in the mechanism of action, their structure activity relationships or even their chemical structures. Even

though the specification may provide for certain exemplary drugs from the group of compounds identified as rapidly precipitating drugs, it does not provide necessary link between finding a particular compound or narrowing the range of candidates in order to find the suitable compounds without the need for undue experimentation.

Second, even though the level of ordinary skill in the art may allow practice of the assays to test compounds having the potential properties claimed, aside from the compounds recited in claim 38, no where in the specification provides any guidance to select compounds that are likely to be of use in practicing the claimed invention. Rather, the specification relies on hypothetical level of ordinary skill in the art to supply the missing information by conducting an assay to identify the rapidly precipitating drug instantly claimed. Given the broad breadth of the claims the ordinary skill in the art would not have any guidance as what type of compounds should he proceed with and thus would be not be in proper notice of the scope of the pending claims.

Further, as it has repeatedly been stressed by the Courts, an assay for determining whether a given compound possesses certain desired characteristics and identifies some broad categories of compound that might work, without more precise guidelines, amount to little more that "a starting point, a direction for further research." Se *Genetech* v. *Novo Nordisk A/S*, 108 F. 3d 1361, 1366, (Fed. Cir.), also *Enzo Biochem, Inc.* V. *Calgene, Inc,* 1888 F. 3d 1362, 1374 (Fed Cir 1999).

....Thus, practicing the entire scope of the instant claims require undue experimentation."

RESPONSE TO EXAMINERS ARGUMENT NO. 1

The fact that a specification may require some trial and error does not mean *per se* that it fails to meet the enablement requirement. *W.L.Gore & Associates, Inc. v. Garlock, Inc.* 220 USPQ 303 (Fed. Cir. 1983).

The instant claims do more than define a trial and error procedure. They clearly define three observable physical characteristics that are common to rapidly precipitating drugs as that term is defined in the specification. First it must be "a fairly soluble or highly soluble salt form of a poorly soluble free base or free acid"; second, it must be able to dissolve rapidly in and form a supersaturated solution in water or simulated physiological fluid at body temperature and third it must begin to rapidly precipitate out of solution within 60 minutes to a less soluble form which provides a concentration that is less than therapeutic. Tests for determining these characteristics can be performed within a reasonable amount of time and one skilled in the art can readily ascertain the results. Such tests for determining whether a compound is capable of forming a supersaturated solution are described in many publications on the solubility of compounds. Such tests are known to be reliable.

The identification of a compound as salt can be made by well known procedures, such as chromatography.

Methods for determining the saturation state of a solution and hence whether a particular solute can form a supersaturated state is well known in the art as is testified to in the declaration of Scott I. Douglas.

The Douglas declaration establishes that whether or not a drug is prone to supersaturation in water or simulated physiological fluids at room temperature can readily be determined without undue experimentation by one skilled in the art. It requires two determinations. First the saturated concentration of the drug in water or simulated physiological

fluids at body temperature must be determined. Second, it must be determined if a concentration of the drug that is higher than the saturation concentration can be obtained in the same volume of water or physiological fluids. If it can, the drug is prone to supersaturation.

The Douglas declaration also provides evidence that procedures for making both of these determinations are conventional in the prior art.

The Examiner has presented no facts or other reasons of record that show that that it would require undue experimentation to determine whether a drug (1) is in salt form, (2) can form a supersaturated solution in water or physiological fluids at body temperature and (3) precipitate from said water or fluids within 60 minutes in to a more insoluble form.

Where all methods needed to practice the claimed invention are in the prior art, the claimed invention is enabled. *Ajinomoto Co., Inc. v. Archer Daniels-Midland,* 56 USPQ 2d,1332 (Fed. Cir.). In the instant case all the techniques required to identify a rapidly precipitating drug are conventional and well-know as is shown by the Douglas declaration.

RESPONSE TO EXAMINER'S ARGUMENT NO. 2

This argument is not well founded. It disregards the instructive nature of the list of compounds described on page 3, lines 21 to 29 of the specification and Claim 70 (original claim 25). The referred to disclosures provide a list of 22 rapidly precipitating drugs. These drugs have a wide variety of therapeutic utilities and chemical structures, but they are linked together by three easily ascertainable physical properties. First, they are fairly soluble or highly soluble salts; second they are capable of generating a supersaturated solution in water or simulated physiological

fluids at body temperature; and third, when introduced in said water or physiological fluids at body temperature, more than 90% of each of these drugs precipitate out within 60 minutes after coming in contact with said water or simulated physiological fluid at body temperature. Whether or not a drug possesses these three characteristics can be determined by one skilled in the art without undue experimentation as is testified to by declarant Douglas.

With respect to the enablement of the full scope of the claims, the scope of claim 68 is no broader than the disclosure. The definitions of "rapidly precipitating drug' in the specification and claim are identical. The term is exemplified by 22 compounds and methods for identifying other rapidly precipitating drugs are set forth in the specification.

Claim 68 is directed to a tablet composition containing a rapidly precipitating drug and testing that does not require undue experimentation can identify that drug, therefore the claim also provides notice to the public of the scope of protection. Amgen v. Chugai Pharmaceuticals Co. 18 USPQ2nd 1016,1027 (Fed. Cir. 1991).

EXAMINER'S ARGUMENT NO. 3

As pointed out above, when an Examiner asserts that a disclosure is non-enabling, the examiner has the burden of establishing such non-enablement. In the instant application, the Examiner has not introduced any evidence as to why the disclosure is non-enabling. For example, he has not introduced evidence showing that the technology for determining whether or not a drug has the three characteristics outlined above, such as a teaching that the technology required to make such determination is unpredictable or would require undue experimentation.

The Examiner cites *Genentech v. Novo Nordisk A/S,* 42 USPQ2d 1001 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Calgene, Inc.*, 52 USPQ 2d 1129 (Fed. Cir. 1999) to support his position.

Neither the *Genentech* nor the *Enzo* case support the Examiner's rejection of the claims under 35 U.S.C. §112, first paragraph.

In *Genentech,* the issue was whether the patentee had enabled a person of ordinary skill in the art to use cleavable fusion expression to make human growth hormone without undue experimentation. The court held that the specification did not disclose:

> "a specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work." (42 USPQ 2d, p. 1004).

In the instant application, 22 compounds are disclosed as rapidly precipitating drugs. Also, specific guidance is disclosed for identifying rapidly precipitating drugs.

Unlike the invention in *Genentech*, the technology useful for identifying drugs for use in the claimed tablet composition is not unpredictable. See *Genetech,* p. 42 USPQ2d 1006, where it is stated:

> "Where, as here, the claimed invention is the application of an unpredictable technology in the early stages of development, an enabling description in the specification must provide those skilled in the art with a specific and useful teaching."

The invention in the *Enzo* case was directed to antisense technology which was useful to block gene expression in a cell. The claims were directed to among other things:

> 1. A prokaryotic or eukaryotic cell containing a non-native DNA construct, which construct produces an RNA which regulates the function of a gene, said DNA construct containing the following operably linked DNA segments:

a. a transcriptional promoter segment;

b. a transcription termination segment; and there between

c. a DNA segment;

* * *

3. A method of regulating the function of a gene in a prokaryotic or eukaryotic cell which comprises introducing into said cell the DNA construct of claim 1.

The specification described how to make three prokaryotic e-coli (prokaryotic) cells, but provided no directions on how to either make any other prokaryotic cells or any eukaryotic cells.

The issue was whether disclosure of how to make three prokaryotic cells of the same material (E.coli) and no eukaryotic cells of any kind enabled a claim to all prokaryotic and eukaryotic cells. In view of the unpredictability of the technology and failure of anyone to make such cells prior to the filing of *Enzo*'s application, the Court held that the claim was not enabled.

The Examiner has introduced no evidence to show that procedures used to determine whether or not a drug is a soluble salt, is prone to supersaturation or determine the precipitation time of drug is unpredictable and hence requires undue experimentation. The use of procedures to determine these physical characteristics does not require undue experimentation as is shown by the declaration of Research Chemist, Scott Douglas.

Declarant Douglas, who is skilled in the art of the preparation of pharmaceutical products, testifies that a rapidly precipitating drug, as that term is defined in the above captioned application, can be identified without undue experimentation.

In the instant application, compounds capable of forming supersaturated solution in water or physiological fluids at body temperature and having the precipitation profiles

required in the claim were known in the art at the time the application was filed. This is shown by the compounds described on page 3, lines 21-29 of the specification and original Claim 25.

The Federal Court has explained what is meant by "undue experimentation" in the following language:

> "(t)he test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention."
>
> *In Re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988), quoting *In Re Angstadt* 190 USPQ 214 (CCPA 1976).

The key word is "undue" not "experimentation".

New Claim 70 is identical to Claim 38, except that it has been written in independent form. It identifies 22 specific compounds and as admitted by the examiner is enabled by the specification.

In summary the claims are enabled as is shown by application of number of the factors set forth in *In re Wands*.

1. The quantity of experimentation necessary - As shown by the declaration of Declarant Douglass, the determination of whether a drug is prone to saturation does not necessitate a large amount of experimentation.

2. The amount of direction or guidance provided - The definition of a rapidly precipitating drug as being a fairly soluble or highly soluble salt of a poorly soluble free base or acid, prone to supersaturation and able to precipitate from solution to a less soluble form within sixty (60) minutes provides ample guidance to one skilled in the art how to identify a rapidly precipitating drug. This is particularly

so because the tests for identifying these three characteristics can be performed without undue experimentation.

3. The presence or absence of working examples - The specification discloses two complete working examples of delavirdine mesylate. It also discloses how much, by weight percent, of the rapidly precipitating drug must be in the claimed tablet composition. Further it identifies twenty two other rapidly precipitating drugs.

4. The relative skill of those in the art - The relative skill of those in the art of pharmaceutical composition manufacturing is high. While the claimed tablet composition is unobvious, nevertheless, one skilled in this art could readily identify rapidly precipitating drugs and readily use them after reading Applicants' disclosure.

5. The breadth of the claims - While the breadth of the claims may be considered broad, it is no broader than the disclosure since the description of a rapidly precipitating drug in the specification is commensurate in scope with the definition in the claim.

THE REJECTION OF CLAIMS 2-20, 22-24, 26, 34, 36-38, 68 AND 69 UNDER 35 U.S.C. §103(A) AS BEING UNPATENTABLE OVER MAKOOI-MOREHEAD ET AL (U.S. PATENT 6 238 695) IN VIEW OF ELGER, ET AL (U.S. PATENT 4 844 907)

Claims 2-20, 22-24, 26, 34, 36-38, 68 and 69 are patentably distinguishable over the combination of Markooi-Morehead et al and Elger et al for the following reasons:

Present Claim 68 is directed to a non-sustained release, non-chewable tablet composition comprising:

(a) a rapidly precipitating drug which is a fairly soluble or highly soluble salt

form of a poorly soluble free base or free acid that is prone to supersaturation when introduced in water or simulated physiological fluid at body temperature, and more than 90% of it precipitates out within 60 min after coming into contact with said water or simulated physiological fluid at body temperature, with the proviso that the drug is not delavirdine mesylate, is the sole active pharmaceutical ingredient in said composition and is present in an amount from about 5 to about 60%;

(b) a polymeric binder in an amount from about 2 to about 25%;

(c) a superdisintegrant in an amount from about 6 to about 40%; and

(d) a lubricant present in an amount up to about 5%.

The unobviousness of the claimed invention resides in applicants' selection (1) of a specific form of the drug (a fairly soluble or highly soluble salt of a poorly soluble free acid or free base) that is prone to supersaturation and (2) a combination of the drug form with specific amounts of a polymeric binder and a super disintegrant that delays precipitation of the drug from the supersaturated solution.

As pointed out in Applicants' prior response, (1) there would be no motivation to combine Makooi-Morehead et al with Elger et al and (2) even if combined the combination would not establish a prima facie case of obviousness.

THERE IS NO MOTIVATION TO COMBINE THE TEACHING OF MAKOOI-MOREHEAD ET AL WITH THE TEACHING OF ELGER ET AL

There is no motivation to combine the teaching of Makooi-Morehead et al with the teaching of Elger et al because

(a) The inventors in the two patents are trying to solve different problems. Makooi-Morehead et al are focused on providing a solid dosage form that will enhance the dissolution rate of an insoluble drug, efavarenz. Elger et al

are focused on providing a multi-phase tablet that contains both a narcotic analgesic and a non-steroidal anti-inflammatory that overcomes prior art problems including serious incompatability, poor crushing strength, long disintegration times and sticking (See column 1, lines 35-40 and column and column 4, lines 8-10).

(b) Makooi-Morehead et als' composition requires the use of a lubricant, such as magnesium stearate in relatively small amounts whereas Elger et al excludes the use of a lubricant and uses instead a self-lubricating compression aid in an amount of 10-90% (See column 5, lines 8-22). Elger et al demonstrates in their comparative examples that their formulations will not work in the presence of a lubricant. Furthermore none of the drugs used in Elger et als' regular examples are fairly soluble salts or highly soluble salts of a poorly soluble free acid or free base.

(c) Makooi-Morehead et al disclose a special tablet composition for a specific drug, efavirenz. They do not suggest that other drugs can be used in the composition.

(d) Makooi-Morehead et al disclose a tablet composition that contains a single drug, efavirenz, whereas the Elger et al composition is a multiphase tablet that contains two drugs; and

(e) The Makooi-Morehead et at composition contains a drug which has utility as an inhibitor of HIV and treatment of AIDS, whereas the Elger et al compositions are disclosed as having synergistic analgesic and anti-inflammatory activity.

In responding to Applicants' argument, the Examiner asserts in the first full paragraph on page 6 of the Office Action:

> "Examiner would like to point out that certain line of reasoning were not commensurate with the scope of pending claims. For example, the use of lubricant in the instant generic claims is in amounts "up to 5%". This amount includes

> 0%-5%. Therefore, Eldger's[sic] lack of using lubricants still fall within the scope of the pending claims."

As stated above, there are at least four other reasons why there would be no motivation to combine Makooi-Morehead et al and Elger et al besides the presence of a lubricant in the Makooi-Morehead composition.

This argument was and is not applicable to claim 24 because it expressly recites that lubricant is present in the amount of 0.25 to 2%.

This argument is also not applicable to amended claim 68 which recites that the lubricant is "present" in an amount up to 5%.

The addition of the word present makes it clear that lubricant is present in an amount above zero. See page 5 lines 20-26 of the instant specification where it is disclosed that:

> "The lubricant is not absolutely necessary to prepare the tablet formulation of the present invention. However, it is highly desirable to have it present in most cases. When present it is preferred that it be selected from the group consisting of magnesium stearate and stearic acid; it is more preferred that the lubricant be magnesium stearate. When present, the lubricant should be present in an amount up to about 5%. It is preferred that the lubricant be present in an amount of 0.25 to about 2%."

Finally, the only pharmaceutical active ingredient disclosed in the tablet composition of the primary reference, Makooi-Morehead et al, is Efavirenz. Efavirenz is not in a fairly soluble or highly soluble salt form, which is a requirement of Claim 68. I am sure that the Examiner can appreciate this fact because in prior discussion on the record there was an issue as to whether or not Efavirenz was an anhydrous free acid or free base. The Examiner took the position that Efavirenz read on an anhydrous free acid or free base. It was agreed that this issue could be removed by deleting references to anhydrous free acids and free bases in the claims and restricting the active ingredient to fairly

soluble or highly soluble salts of poorly soluble free acids or free bases. This deletion was made in amendments contained in the response to the prior Office Action.

As recognized by the Examiner, the purpose of the Makooi-Morehead, et al formulation is to:

> "improve the rate of dissolution and thus the extent of absorption in the GI-track (column 2, lines 3-7)."

The primary reason that Applicants use a soluble salt is to increase the amount of drug that goes into solution and not the rate that it goes into solution. The fairly soluble or highly salt provides a drug form that is capable of forming a supersaturated solution and the polymeric binder and super disintegrant in the claimed tablet composition delays precipitation of the drug thereby providing a much higher concentration of drug for absorption in the small intestine.

Efavirenz is not in salt form, which is a requirement of Claim 68. There is nothing in Makooi-Morehead, et al that either teaches or suggests that a salt form of Efavirenz can be used in the tablets described therein.

Further, Makooi-Morehead et al does not disclose the use of a polymeric binder as has been pointed out by Applicant in previous responses.

THE COMBINATION OF MAKOOI-MOREHEAD ET AL AND ELGER ET AL DOES NOT ESTABLISH A PRIMA FACIE CASE OF OBVIOUSNESS AGAINST THE CLAIMED COMPOSITION

Even if there was motivation to combine Makooi-Morehead et al and Elger et al, the combination would not render claim 68 obvious for the following reasons.

Since the Makooi-Morehead et al tablet composition contains efervarenz, an insoluble drug, one skilled in the art would be led to only use the insoluble forms of drugs disclosed in Elger et al and not fairly soluble or highly soluble salt forms of insoluble drugs. Failure to utilize a

fairly soluble or highly soluble salt of a poorly soluble drug would result in a tablet that does not meet all of the limitations of claim 68.

Since Elger et al discloses a synergistic bi-layered drug, one skilled in the art would be led to substitute two drugs, a narcotic analgesic and an anti-inflammatory for efevirenz. Such a combination is excluded from the claimed tablet composition because it is limited to a single pharmaceutical active ingredient.

Utilizing components from the individual layers of the Elger et al tablet in combination with Makooi-Morehead et al would also not render the instant claims obvious for the following reasons. The narcotics analgesic phase of Elger et al does not include a disintegrant and all of the exemplified tablet compositions (Examples 1-13) utilize highly soluble narcotic drugs (codeine and hydrocodeine) rather than poorly soluble narcotic drugs. The non-steroidal anti-inflammatory phase drugs are poorly soluble acids (ibuprofen-Examples 1-11; naproxen-Example 12 and flurbiprofen-Example 13) and not a fairly soluble or highly soluble acid of a poorly soluble drug.

The most preferred drugs of Elger et at are codeine phosphate and ibuprofen (free acid), column 3, lines 11-15. Both codeine(1g/20 ml of water) and codeine phosphate (freely soluble) are very soluble in water. See Merck Index, 10th Edition. Ibuprofen free acid is relatively insoluble in water, Merck Index, Tenth Edition. Therefore neither codeine phosphate nor ibuprofen are fairly soluble or highly soluble salts of a poorly soluble free acid or free base and hence will not form a supersaturated solution in water or simulated physiological fluids at body temperature.

Neither Makooi-Morehead et al nor Elger et al recognized the advantage of utilizing a fairly soluble or highly soluble salt of a poorly soluble free acid or free base. This is

shown by Makooi-Morehead et al's use of poorly soluble Efavirenz and Elger et al's failure to discriminate between using a more soluble salt form of a poorly soluble drug rather than using the poorly soluble drug itself. See the list of active ingredients in the Table shown in Column 2 of Elger et al.

The Examiner also alleges that there is a reasonable chance of success with utilizing the combined teaching of Elger et al and Makooi-Morehead et al. However, this allegation is not supported by Elger et al because they disclosed in their comparative examples that when a lubricant was used the compressed tablets prepared thereby exhibited poor quality.

Hence, the combination of Makooi-Morehead et al and Elger et al does not establish a prima facie case of obviousness against claim 68.

Claims 2-20, 22-24, 24,26, 34, 36 and 37 contain all of the limitation of Claim 68, so they are patentable over the combination of Makooi-Morehead et al for the reason that Claim 68 is and because they contain additional limitations that further define over the combination of references.

Present Claim 69 differs from Claim 68 in that it (1) does not require a lubricant and (2) adds the limitation "without heating, solvent or grinding". It is patentably distinguishable over the combination of Makooi-Morehead et al and Elger et al for most the reasons that claim 68 is patentably distinguishable over them and also because it excludes the use of wet granulation (water, when present, functions as a solvent).

In view of the above amendments and arguments, withdrawal of the rejections and expeditious passage of this application to issue is respectfully solicited.

Respectfully submitted,

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